Please amend Claim 30 as follows:

30. A method of treating multidrug resistance, comprising administering to a mammal in need of such treatment the composition according to Claim 11.

Please amend Claim 31 as follows:

31. A method of treating multidrug resistance, comprising administering to a mammal in need of such treatment the composition according to Claim 24.

REMARKS

Upon entry of the amendments herein, Claims 2, 4, 9, 11, 18 – 25, and 27 – 31 will be pending. Claims 5 and 26 have been cancelled.

Among other amendments to the claim as described herein, Claim 18 has been amended to correct typographical errors at subsection (f) of the claim. In particular, the terms "–$NR^6(R^7)$- " and "-O_rR^6- " have been amended for clarification to read "–$NR^6(R^7)$" and "-O_rR^6", respectively. Support for this amendment is found in the specification at page 9, lines 17 and 18.

Remaining remarks are as follows:

The Election of Species Requirement

Applicants traverse this requirement. The Examiner has merely concluded that the claimed compounds include distinct linking groups "R^4" and the distinct terminating groups "R^5". The Examiner has not indicated any further reasons for the requirement, such as an undue search burden. Notwithstanding, Applicants confirm the provisional election of Compound Number 7, appearing on page 34 of the present specification. As the Examiner has noted, this compound is also the first pictured compound of Claim 24.

The Claim Objections

The Examiner has objected to Claim 26 as being of improper dependent form. This claim has been cancelled. The rejection is now moot and should be withdrawn.

The Rejections Under 35 U.S.C. § 112

First Rejection (Section 8 of the Office Action)

The Examiner continues to reject Claims 2, 4, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that use of the term "about" with reference to indivisible terms is indefinite.

Applicants again respectfully traverse this rejection. The Examiner appears concerned that the term "about" could be interpreted to mean "10.1 or 9.9 atoms" rather than a whole number. As recognized by the Examiner, this is not technically possible. Indeed, the ordinarily skilled artisan will readily understand that the term "about" in the recited instances will relate to whole numbers of atoms or other groups, not fractions.

Indeed, Applicants remain unaware of any precedent which precludes the use of "about" in the cited instances, including those instances where only whole numbers are appropriate. To the contrary, use of the term "about" to modify a quantitative description is commonplace throughout the chemical patent arts. Indeed, the Patent Office has routinely allowed and granted patents that contain claims utilizing the term "about" to modify a quantitative description, even where the quantitative description is an indivisible whole number. For example, Chatterjee, U.S. Patent No. 6,329,377, issued December 11, 2001 and Gangjee, U.S. Patent No. 6,221,872, issued April 24, 2001, both of which list Mukund J. Shah as the relevant Patent Office Examiner, utilize the term "about" to modify indivisible chemical chain lengths. The context of usage in these granted patents is no different relative to Applicants' current usage. Indeed, the Examiner is imposing prejudice with respect to the present patent application in improperly disregarding rules of practice that are routinely utilized in the examination of patent applications.

The Examiner cites *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 Fed. Cir. 1991, in support of the rejection. In doing so, the Examiner cites various passages from *Amgen* that relate to the specific factual circumstances in that case. For example, in *Amgen*, the Federal Circuit found that the existence of close prior art, coupled with testimōny offered by the parties, was determinative in finding the relevant claims indefinite due to the use of the term "about." However, in doing so, the Examiner fails to relate the relevance of the *Amgen* prior art issue, as well as the *Amgen* testimony, to Applicants' claimed subject matter. Indeed, none of these factual circumstances are present with respect to the patent application currently before the Examiner.

Moreover, the Examiner fails to recognize that the Federal Circuit expressly limited the decision in *Amgen* to the specific facts set forth therein. Importantly, the Federal Circuit states that "[i]n arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims." See *Amgen*, p. 1218 (emphasis added).

As has been stated, and as the Examiner is compelled to recognize and accept, use of the term "about" to modify various claim limitations has been found to be routinely acceptable in the chemical arts. See *W.L. Gore & Associates v. Garlock, Inc.*, 842 F.2d 1275 (1988). In rejecting this established rule, it appears that the Examiner is attempting to resolve issues that have been found to be matters of law reserved for the courts through procedures such as *Markman* hearings. See *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (1996). In doing so, particularly since the Examiner has failed to present a nexus between the present rejection and any prior art issue (as with *Amgen*), the Examiner is respectfully acting outside the scope of his authority.

For example, the Examiner is compelled to recognize the procedures and holding set forth in *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211 (Fed. Cir. 1995). In *Pall*, the Federal Circuit did not dispute whether use of the term "about" was appropriate, but rather recognized that claim construction was the issue, an issue which was a matter of law settled by the relevant court in view of extrinsic and other evidence. The Federal Circuit stated:

> The district court, construing the term 'about 5:1 to about 7:1,' observed that the word 'about' does not have a universal meaning in patent claims, and that the meaning depends on the technological facts of the particular case. We have so held. . . . [citing *W.L. Gore & Associates v. Garlock, Inc.*, 842 F.2d 1275 (1988)]. . . . The determination of whether the literal meaning or cope of 'about 5:1 to about 7:1' includes 4:1 is a matter of claim construction, a question of law for decision *de novo* by this court. The use of the word 'about,' avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technologic and stylistic context. . . . Extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter, and may be received from the inventor and others skilled in the field of the invention."

See *Pall*, p. 1217.

Moreover, the Federal Circuit continues to recognize the appropriate use of the term "about" in a granted patent claim, and the role of the courts with respect to interpretation. *Modine Manufacturing Co. v. U.S. International Trade Commission*, 75 F.3d 1545 (Fed. Cir. 1996) stated:

> The specification uses the qualifier "about," and also states that the optimum hydraulic diameter varies with the conditions. Such broadening usages as "about" must be given reasonable scope; they must be viewed by the decisionmaker [the court, *e.g.*, pursuant to a *Markman* hearing] as they would be understood by persons experienced in the field of the invention. . . . Although it is rarely feasible to attach a precise limit to "about," the usage can usually be understood in light of the technology embodied in the invention.

See *Modine*, p. 1554.

In view of binding precedent, therefore, Applicants' claims duly meet the requirements of 35 U.S.C. § 112, second paragraph. The Examiner is compelled to follow the ready acceptance of the term "about" by the Federal Circuit, particularly absent the precise factual issues present in *Amgen*, with the understanding that it is not the Examiner's role to interpret the precise scope of the claim. The Examiner should recognize that these matters have been clearly reserved for the courts, a responsibility which is not properly the Examiner's concern in this instance. Respectfully, it is for all of the above reasons that the Examiner should withdraw the rejection of Claims 2, 4, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, second paragraph.

Second Rejection (Section 9 of the Office Action)

The Examiner has rejected Claims 29 – 31 based on inclusion of language relating to treatment of a mammal in need of inhibition of p-glycoprotein or MRP1. While Applicants traverse this rejection as ample teachings have been provided in the specification, Applicants have amended Claims 29 – 31 to delete reference to p-glycoprotein and MRP1 in order to narrowly frame the issues remaining for prosecution. The rejection is moot and should be withdrawn.

Third Rejection (Section 10 of the Office Action)

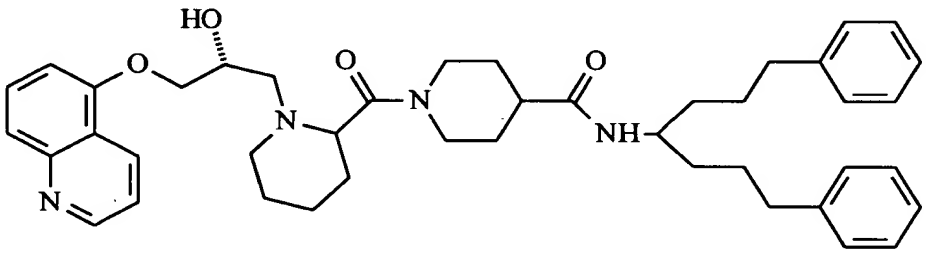
The Examiner has rejected Claims 2, 4, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant are that the inventors had possession of the claimed invention. Specifically, the Examiner objects to the language regarding amides, esters, and imides susceptible to being cleaved *in vivo* by a mammalian subject. While Applicants reiterate arguments made in previous responses to the Examiner, Applicants have deleted this language as set forth in Claim 18 in order to simplify the issues remaining for prosecution. All dependent claims are affected by this deletion. Accordingly, this rejection is now moot and should be withdrawn.

Fourth Rejection (Section 11 of the Office Action)

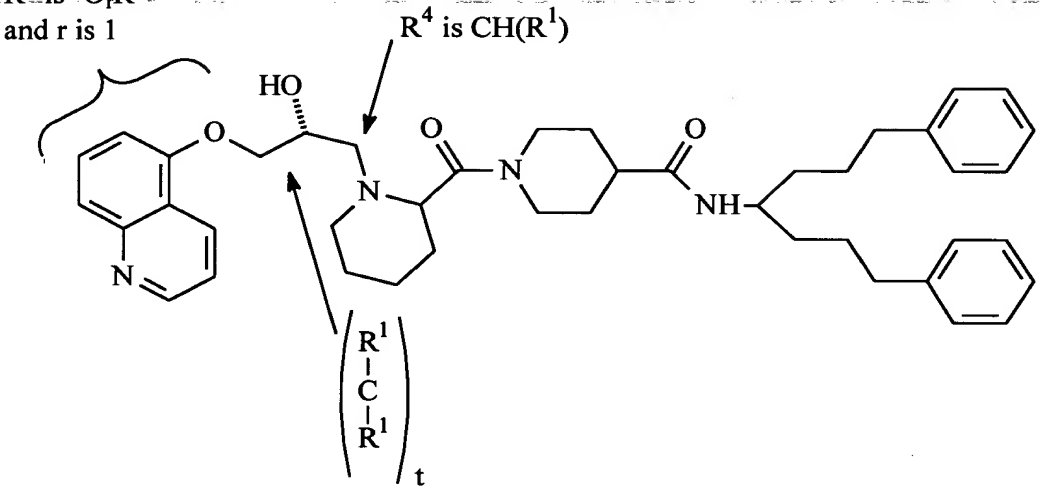
The Examiner continues to reject Claims 2, 4, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, first paragraph. The Examiner states that "[t]he proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 lacks description. Nowhere in the specification is such a relationship linking the description between the two radicals described. The concept of linking the value of r to the specific divalent radical present as R^4 is not present."

The Examiner argues: "until the Examiner made the anticipation rejection, the Applicant had no reason to single out the species embraced by the provisos." This conclusion is flawed for several reasons, for example: 1) the Examiner assumes that the species embraced by the provisos are not important to Applicants, despite the fact that each element of the proviso is explicitly set forth at page 12, lines 17 and 18 of the present specification; and 2) there is no rule or other tenet of law that requires a patent Applicant to provide the Examiner a "reason" for any amendment made during prosecution.

In amending the claims to require the relevant proviso (*i.e.*, "with the proviso that wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6-$ then r is 1"), Applicants noted that this proviso was fully supported by the specification such as, for example, at Example 7 at page 34 (which is actually Applicants' provisionally elected species). Applicants maintain this assertion. Full support for this proviso is indeed set forth at this location of the specification; indeed, Example 7 describes the following compound:



Each element of the relevant proviso is described by the structure, as is seen from the following notations:



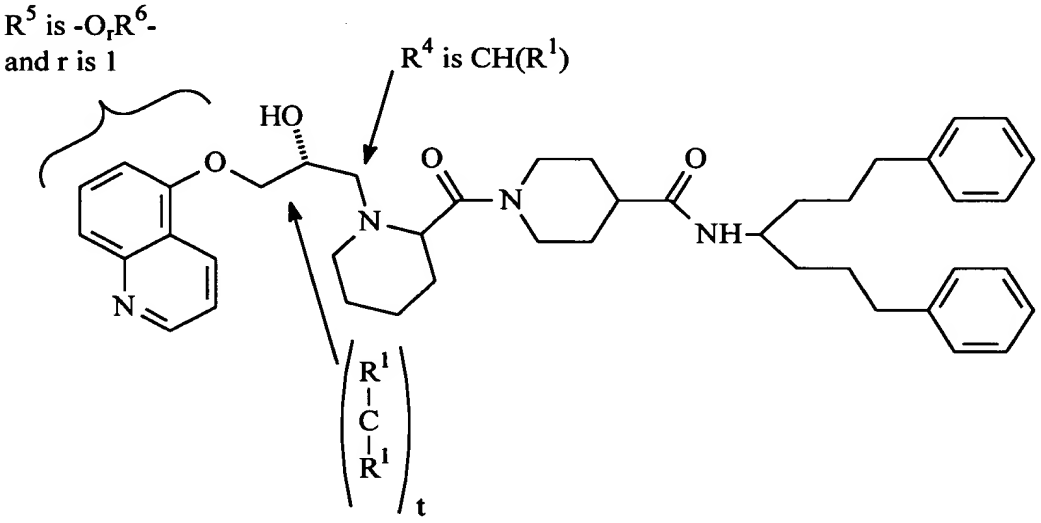
In particular, in this structure set forth in the specification, R^4 is $-CH(R^1)-$, R^5 is $-O_rR^6-$ and r is 1, thereby describing each and every element of the relevant proviso. That each and every element may not be described *in words*, "verbatim" as the Examiner has characterized it, is immaterial. The description exists in the specification. This proviso has therefore been adequately and, indeed, quite explicitly, set forth in the specification as filed. Applicants therefore request that the Examiner withdraw the rejection of Claims 2, 4, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, first paragraph.

The Rejection Under 35 U.S.C. § 102(b)

The Rejection Based on Xue

The Examiner continues to reject Claims 2, 4, 11, 18, and 25 – 27 under 35 U.S.C. §102(b) based on Xue *et al.*, WO 99/65867, published December 23, 1999 (herein referred to as "Xue"). The Examiner states that although the amendments presented by Applicants in their response dated March 19, 2002 overcome the rejection in terms of anticipation, the rejection is maintained based on the "new matter" rejection set forth in the Fourth Rejection of the Office Action (Section 11 of the Office Action).

As Applicants have explained above with respect to this Fourth Rejection, the proviso set forth in Claim 18 that excludes the subject matter of Xue is adequately described in the specification and therefore does not include new matter. In particular, as described above and reiterated here, full support for this proviso is set forth at Example 7, page 34 of the present specification. Indeed, each element of the relevant proviso is described by the structure, as is seen from the following notations:



In particular, in this structure set forth in the specification, R^4 is $-CH(R^1)-$, R^5 is $-O_rR^6-$ and r is 1, thereby describing each and every element of the relevant proviso. Accordingly, the proviso as set forth in Claim 18 is fully described in the specification.

Moreover, it is improper to maintain the present rejection because the Examiner has acknowledged that the recited compound does not anticipate the claims as amended. "New matter" is not an appropriate basis for a rejection based on anticipation. Since the claim amendments *have been entered*, the present rejection based on 35 U.S.C. § 102(b) should be promptly withdrawn.

The Rejection Based on Sato

The Examiner has reinstated the rejection of Claims 2, 18, and 25 under 35 U.S.C. §102(b) based on Sato *et al.*, U.S. Patent 5,506,239, issued April 9, 1996 (herein referred to as "Sato"). The Examiner cites one compound from Sato, stating that this compound anticipates Applicants' claims. The compound contains an unsubstituted piperidine ring which forms an amide linkage with a core pyrrolidine ring structure.

The Examiner stated on the Office Action dated October 29, 2002 that the requirement for a substituted piperidine ring formed by R^2 and R^3 overcame the previous rejection, but that the requirement was only set forth in Applicants' dependent Claim 4 rather than the corresponding independent ("parent") claim. Respectfully, Applicants believe that the Examiner has overlooked the recitations of independent Claim 18, which require at subsection (d) that R^2 and R^3 are bonded together to form a substituted piperidyl. Accordingly, as follows, the present invention is not anticipated by Sato.

As is set forth in independent Claim 18, the pyridine ring formed by the linkage of R^2 and R^3 is *substituted* (Claim 18 states that R^2 and R^3 are bonded together to form a substituted piperidyl). As set forth in the present specification, one or more hydrogen atoms bonded to *carbon atoms* in the ring are replaced with other substituents in a substituted heterocyclic group (*e.g.*, a substituted piperidyl). As such, in addition to the linkage to the $C(R^1)(R^1)_x$ moiety, or wherein x is 0 then the core ring structure A, the piperidine ring formed by R^2 and R^3 must be substituted with some other moiety at any of the carbon atoms of the ring. See specification at page 6, lines 10 – 14; page 8, lines 1 – 11; and page 9, lines 13 and 14. As evident based on Applicants' independent Claim 18, this requirement for a *substituted* heterocyclic ring structure formed by R^2 and R^3 is not optional but rather a required element of the present invention.

In contrast, the cited structure set forth in Sato fails to describe or suggest a substituted piperidine ring structure. As such, Applicants' claims are novel and patentable over Sato, and the rejection should be withdrawn.

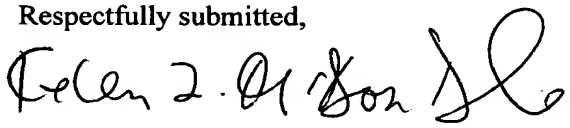
The Rejection Based on Grell

The Examiner has rejected Claims 2, 4, 18, and 25 based on Grell, DE 195 48 797 A1 (herein referred to as "Grell"). The Examiner cites a compound disclosed in Grell which contains a sulfonyl moiety, purported by the Examiner to be equivalent to "R^4." In view of the present amendments to Claim 18, and the corresponding cancellation of Claim 5, Applicants assert that this reference fails to anticipate the presently claimed invention. Indeed, amended independent Claim 18, upon which all of the present claims depend, does not include sulfonyl among the selected moieties for R^4, but rather utilizes -C(O)C(O)- or $-CH(R^1)-$. Grell, including the recited example and disclosure as a whole, therefore fails to anticipate the claims as amended herein. As such, Applicants' claims are novel and patentable over Grell, and the rejection should be withdrawn as moot.

CONCLUSION

Applicants therefore respectfully request that the Examiner withdraw the rejections under 35 U.S.C. §§ 102(b) and 112 and allow Claims 2, 4, 9, 11, 18 – 25, and 27 – 31 as amended herein (Claims 5 and 26 having been cancelled). If the Examiner believes that personal contact would be beneficial for disposition of the present application, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,



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January 2, 2003
Mason, Ohio

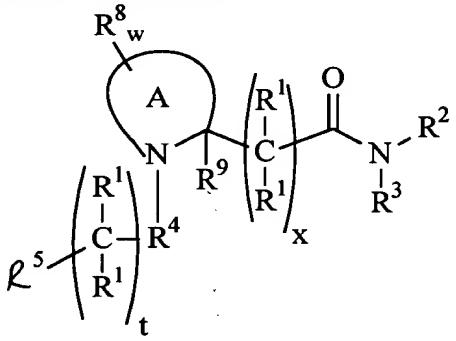
Customer No. 27752

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 5 has been cancelled.

Claim 18 has been amended as follows:

18. A compound having the structure:



or an optical isomer, diastereomer, enantiomer, pharmaceutically-acceptable salt~~, amide, ester, or imide susceptible to being cleaved *in vivo* by a mammalian subject to yield the compound~~ thereof, wherein:

(a) w is 0 to about 6, x is 0 to about 10, and t is 0 to about 6;

(b) A is a substituted heterocyclic group having about 4 to about 9 members;

(c) R^1 is selected from the group consisting of a hydrogen atom, a hydroxyl group, a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;

(d) R^2 and R^3 are bonded together to form a substituted piperidyl;

(e) R^4 is selected from the group consisting of ~~$-S(O)_2-$~~, ~~$-$~~C(O)-C(O)~~$-$~~, and $-CH(R^1)-$;

(f) R^5 is selected from the group consisting of $-NR^6(R^7)-$ and $-O_rR^6-$, wherein r is 0 or 1; with the proviso that wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6-$ then r is 1;

(g) R^6 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted

heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and

R^7 is selected from the group consisting of a hydrogen atom and R^6;

(h) R^8 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and

(i) R^9 is selected from the group consisting of a hydrogen atom and a hydrocarbon group.

Claim 26 has been cancelled.

Claim 29 has been amended as follows:

29. A method ~~selected from the group consisting~~ of treating multidrug resistance, ~~inhibiting p-glycoprotein, inhibiting MRP1, and combinations thereof,~~ comprising administering to a mammal in need of such treatment ~~or inhibition~~ the composition according to Claim 18.

Claim 30 has been amended as follows:

30. A method ~~selected from the group consisting~~ of treating multidrug resistance, ~~inhibiting p-glycoprotein, inhibiting MRP1, and combinations thereof,~~ comprising administering to a mammal in need of such treatment ~~or inhibition~~ the composition according to Claim 11.

Claim 31 has been amended as follows:

31. A method ~~selected from the group consisting~~ of treating multidrug resistance, ~~inhibiting p-glycoprotein, inhibiting MRP1, and combinations thereof,~~ comprising administering to a mammal in need of such treatment ~~or inhibition~~ the composition according to Claim 24.